The Neurohospitalist
2016, Vol. 6(2) 80-86

DOI: 10.1177/1941874415605879
nhos.sagepub.com
SAGE

Intracranial Aneurysms From Presumed Infective Endocarditis: The Dilemma of Persistently Negative Cultures

Jason Lockrow, MD, PhD[1], Will Longstreth, MD[1], and Arielle P. Davis, MD[1]

Case History

Paramedics were called when a 39-year-old man had a witnessed generalized tonic–clonic seizure. They found him comatose with a fixed and dilated left pupil and performed emergent endotracheal intubation. On arrival to the hospital, he was afebrile. His blood pressure was 175/125 mm Hg, pulse 86 beats per minute, and oxygen saturation, 100% on 100% Fio_2. He had complained to his wife earlier in the day of headaches and "feeling hypertensive." Although prescribed a thiazide and angiotensin-converting enzyme inhibitor for hypertension, he was nonadherent and his hypertension was poorly controlled. His past medical history was otherwise unremarkable. He had emigrated from Mexico 2 years earlier and worked preparing food. General examination demonstrated an obese middle-aged man. He had a regular rhythm without murmur and had no skin or nail lesions. Neurologic examination revealed a Glasgow Coma Scale of 4 for extensor posturing, and his pupils were now 7 mm bilaterally and unresponsive to light.

Admission laboratory studies were notable for a white blood count of 1120/μL (reference 4.3-10 thousand/μL), a sodium level of 134 mEq/L (136-145 mEq/L), and a potassium level of 2.9 mEq/L (3.5-5.5 mEq/L). Head computed tomography (CT) revealed a left parietal intraparenchymal hemorrhage and subdural hematoma with midline shift and concern for transtentorial and uncal herniation (Figure 1A and B). Computed tomography angiogram (CTA) revealed a focus of hyperattenuation in the hemorrhage during the arterial phase, but not in the postcontrast CT, concerning for an aneurysm or vascular malformation rather than extravasation (Figure 1C and D). He was taken for emergent hemicraniectomy with clot evacuation. Clot cultures remained negative, and the pathology was inconclusive.

Postoperatively, he developed fever, for which blood and urine cultures were obtained. He received 24 hours of postoperative cefazolin and defervesced. He remained without eye opening or spontaneous movement and with extensor posturing, right more than left. Electroencephalography monitoring revealed moderate-to-severe slowing without seizures. Magnetic resonance imaging demonstrated the resection cavity and ischemic consequences of herniation, and a catheter angiogram demonstrated an additional unruptured aneurysm, which in retrospect was evident on the CTA (Figure 1E-H). On postoperative day 2, he was transferred to the Neurology service for management and investigation for the cause of his hemorrhage.

He continued to be intermittently febrile, despite negative cultures, and on hospital day 4, he was started on broad-spectrum antibiotics with vancomycin and meropenem. Upon further questioning, his wife reported him having occasional fevers over the past several weeks. His erythrocyte sedimentation rate and C-reactive protein levels were both elevated based on his age, at 45 mm/h (reference 0-20) and 151 mg/L (reference 0-78), respectively. Although a transthoracic echocardiogram was unrevealing, a transesophageal echocardiogram on day 6 of hospitalization revealed 2 small mobile mitral valve vegetations (Figure 2). Upon consultation with infectious disease, his antibiotics were broadened to vancomycin, cefepime, and gentamycin. By hospital day 4, 3 sets of blood cultures drawn prior to broad-spectrum antibiotics remained without growth.

Differential Diagnosis

Discussant: Jason Lockrow

While intraparenchymal hemorrhage has a broad differential, aneurysm in the setting of infective endocarditis was the prime concern, given the patient's intermittent fevers, distal cerebral aneurysms—both ruptured and unruptured—and the mitral valve vegetations. While his negative blood cultures

[1] Department of Neurology, University of Washington, Seattle, WA, USA

Corresponding Author:
Arielle Davis, MD, Department of Neurology, Box 359775, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104, USA.
Email: apd77@uw.edu

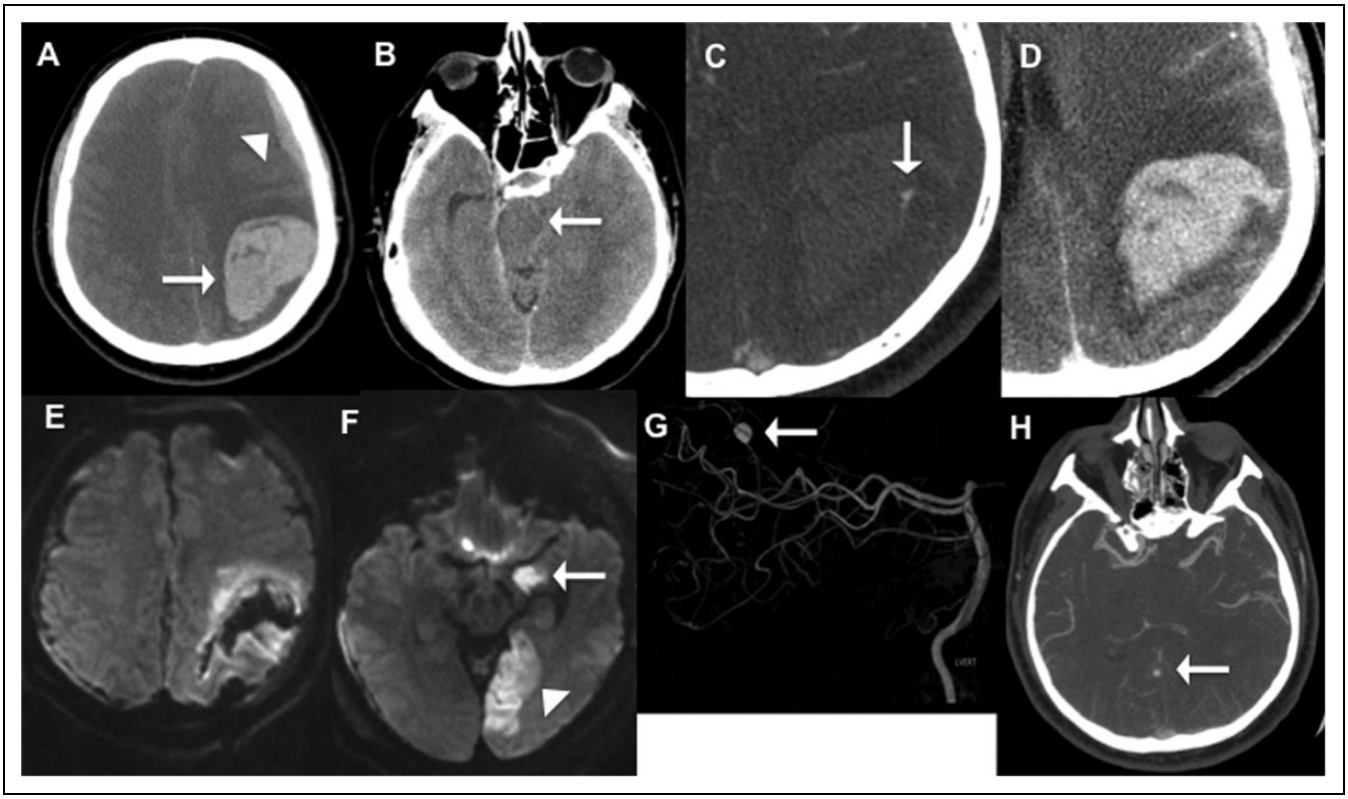

Figure 1. Brain and vessel imaging. Axial noncontrast head computed tomography (CT) on admission with a large left parietal intraparenchymal hemorrhage (arrow) and left frontal subdural hematoma (arrowhead; Panel A) with developing left to right midline shift and left uncal herniation (Panel B). CT angiogram, arterial phase with a focus of hyperattenuation (arrow) within the lateral margin of the hemorrhage concerning for a distal infectious aneurysm (Panel C). Postcontrast scan showed no extravasation of contrast in this same area seen as hyperattenuated on the computed tomography angiogram (CTA) arterial phase, suggesting the contrast was in a vascular structure (Panel D). MRI brain diffusion images demonstrating the evolving left parietal hematoma after evacuation (Panel E), and consequences of herniation: infarcts of the left uncus (arrow) and left posterior cerebral artery distribution (arrowhead; Panel F). Subsequent catheter angiogram with a left vertebral injection confirms a distal right posterior cerebral artery 4.8 × 5.6 mm aneurysm (Panel G), which in retrospect was seen on the admission CTA (arrow; Panel H).

precluded him from meeting a definite clinical diagnosis of endocarditis by Duke criteria (Table 1), he met criteria for a possible diagnosis, given his endocardial involvement, fevers, and evidence of vascular phenomena.

Neurologic sequelae occur in roughly 30% of patients with endocarditis and can be the presenting symptom in half of these cases.[1] While strokes secondary to thromboembolism are the most common neurologic manifestation, aneurysms are a potentially devastating complication, noted in 2% to 4% of infective patients with endocarditis but may be underdiagnosed due to their asymptomatic nature.[1-3] In the past, such aneurysms have been termed "mycotic" although "infective" or "infectious" would be more appropriate. For consistency, we will use the term "infectious aneurysms." Rupture of infectious intracranial aneurysms leads to mortality rates as high as 80%.[4] These aneurysms frequently occur in the distal branches at bifurcation sites in the middle cerebral artery, although posterior cerebral artery aneurysms also occur.[5] Multiple intracranial aneurysms are observed in 25% of cases.[6] The etiology of infectious intracranial aneurysms reflects endocarditis causes, with *Streptococcus viridans* and *Staphylococcus aureus* as the predominant isolates.[7] Negative cultures have been seen in up to 13% of infectious intracranial aneurysms, although those with partial antibiotic treatment were not excluded.[8] In the setting of possible endocarditis and negative blood cultures, it is critical to identify the causative organism, as etiology dictates appropriate treatment.

Etiologies of Endocarditis

Noninfective Endocarditis

In cases where repeat cultures and alternative methods of searching for infectious etiologies remain negative, noninfective or nonbacterial thrombotic endocarditis is worth considering (Table 2). Noninfective endocarditis is associated with autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosis (SLE), which together are known as Libman-Sacks endocarditis, as well as hypercoagulable states, such as malignancy, which is known as marantic endocarditis. Rheumatoid arthritis can be screened for with rheumatoid factor antibodies, while testing for SLE includes

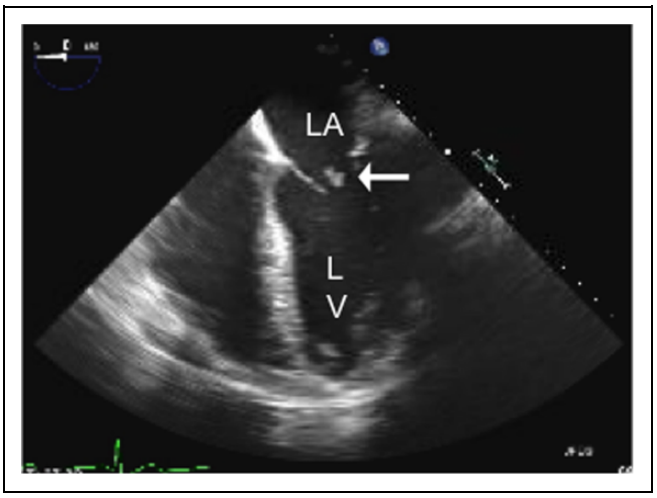

Figure 2. Transesophageal echocardiogram. Four chamber view of the heart showing the left atrium (LA), left ventricle (LV), and mitral valve demonstrating small mobile vegetations present on both leaflets of the mitral valve. Arrow points to the larger vegetation. The initial transthoracic echocardiogram did not reveal these vegetations.

antinuclear and anti-DNA antibodies. When positive, these initial screens necessitate a more thorough rheumatologic evaluation, although diagnosis of Libman-Sacks endocarditis usually requires valvular biopsy. Similarly, marantic endocarditis often requires tissue for diagnosis. A recent study found that confirmed noninfective causes makeup 3% of culture-negative endocarditis and that valvular biopsy was needed to make a diagnosis in more than 40% (5 of 12 patients) of rheumatologic etiologies and in all of the marantic.[10] Aneurysm formation, however, would not be expected in noninfective endocarditis, and hence the presence of aneurysm in our patient suggests an infective etiology.

Infective Culture-Positive Endocarditis

The widely accepted Duke criteria for the diagnosis of infective endocarditis include positive blood cultures (Table 1). Gram-positive cocci are the most frequent isolate. *Staphylococcus aureus*, either methicillin sensitive or resistant, and *S viridans* are the most common pathogens, with *S viridans* more frequent with native valves and *S aureus* with prosthetic values. Other gram-positive bacteria—including coagulase-negative staphylococci, enterococci, and *Streptococci bovis*—are frequently observed and, along with *S viridans* and *S aureus*, makeup as many as 72% to 82% of infective endocarditis cases and more than 90% of those returning positive cultures (Table 2).[15-17] The Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella (HACEK) organisms (see Table 2), a group of fastidious gram-negative bacteria that often require 3 to 5 days of culture incubation to isolate, are the next most common cause of culture-positive endocarditis but account for only 2% to 3% of overall cases.

Table 1. Modified Duke Criteria for the Diagnosis of Infective Endocarditis.[a]

Definite diagnosis requires one of the following:
1. Direct pathologic evidence of infective endocarditis
2. Two major clinical criteria
3. One major and three minor
4. Five minor criteria

Possible diagnosis when any of the following are present:
1. One major and one minor clinical criterion
2. Three minor criteria

Major clinical criteria

Microbiological evidence
- Typical infective endocarditis microorganisms from 2 separate blood cultures without an alternative primary infective focus or
- Microorganisms consistent with infective endocarditis growing from persistently positive blood cultures; at least 2 blood samples drawn >12 hours apart, or growth from 3 of 3 or a majority of ≥ 4 separate blood cultures (with first and last samples drawn at least 1 hour apart)
- Single positive blood culture for *Coxiella burnetii* or *C burnetii* IgG or antibody titer > 1: 800

Evidence of endocardial involvement
- Echocardiogram (either TTE or TEE) with an oscillating or pendulum-like intracardiac mass on the valve or supporting structures, in the path of regurgitant jets, or on implanted material; or abscess; or new prosthetic valve partial dehiscence; or new valvular regurgitation

Minor clinical criteria
- Predisposition to infective endocarditis; predisposing heart condition or intravenous drug use
- Temperature > 38°C
- Microbiological evidence: positive blood culture, not meeting major criteria or serological evidence of active infection with an organism consistent with infective endocarditis
- Presence of vascular sequela, such as major arterial emboli, septic pulmonary infarcts, infective aneurysm, intracranial hemorrhage, conjunctival hemorrhage, and Janeway lesions
- Presence of immunologic phenomena, such as glomerulonephritis, Osler nodes, Roth's spots, or positive rheumatoid factor

Abbreviations: TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.
[a]Adapted from Li et al.[18]

Infective Culture-Negative Endocarditis

Infective endocarditis is considered culture negative when 3 or more independent blood cultures collected over 48 hours remain without growth after a prolonged incubation of at least 7 days.[19] Cultures may be negative for a variety of reasons, but the most common, nearly 50% in some studies,[16] is treatment with antibiotics prior to cultures being drawn. Poor microbiology techniques and holding cultures for insufficient amounts of time can also diminish the yield, but even with proper techniques, roughly 10% of endocarditis remains culture negative. Prolonged negative cultures in the absence of prior treatment necessitate evaluation for alternate infective etiologies,

Table 2. Etiologies of Endocarditis.

Infective culture-positive endocarditis[9,a]		87%
Viridans group streptococci	32%	
Staphlococcus aureus	22%	
Methicillin-resistant *S aureus*	3% of total	
Streptococcus species[b]	22%	
Enterococci	10%	
Coagulase-negative staphylococci	7%	
HACEK[c]	4%	
Anaerobic microorganisms	1%	
Fungi	<1%	
Infective culture-negative endocarditis[10-14]		10%
Coxiella species	3.2%-37.0%	
Bartonella species	9.5%-28.4%	
Staphylococcus species	2.0%-11.1%	
Steptococcus species	3.2%-6.3%	
Fungi	0%-6.3%	
Tropheryma whipplei	0%-2.6%	
HACEK bacteria	0%-3.2%	
Chlamydia species	0%-2.2%	
No identified etiology	22.1%-82.9%	
Noninfective endocarditis[10]		3%
Libman-Sacks endocarditis[d]	39%	
Marantic endocarditis[d]	61%	

[a]In patients with native valve, community acquired infective endocarditis.
[b]Streptococcal species include *Streptococci bovis* (10%), *Streptococci pneumoniae* (2%), β-hemolytic species (5%), other streptococci (1%), nutritionally variant streptococci (1%).
[c]Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella organisms.
[d]Noninfective cases were based on small numbers, only 19 of 759 cases.

including fungi and fastidious and intracellular organisms such as streptococci variants, the gram-negative bacilli of the HACEK group, *Coxiella burnetti*, *Bartonella* species, and *Tropheryma whipplei*.

Fungal causes of endocarditis are rare, under 2% in the general population, though their rates are significantly higher in individuals with previous heart valve surgeries, prolonged antibiotics, intravenous drug use, or immunosuppression.[15,20] Blood cultures are only diagnostic in 50% to 75% of cases of *Candida albicans*, and this rate is even lower with other candidal species. Consequently, these culture-negative cases require serologies—such as antimannan antibodies for Candidal species and galactomannan antibodies for *Aspergillus*—or broad-range fungal polymerase chain reaction (PCR).[21] An older review of infective aneurysms from 1957 to 1987 identified in 20 of 149 patients with fungal aneurysms, but only 5 of these were due to endocarditis, and meningitis was the more common cause of fungal aneurysms.[8]

Challenges of Culture-Negative Endocarditis

The incidence of culture-negative endocarditis varies considerably. While some variability between studies results from incomplete exclusion of patients receiving previous antibiotics, variability is also in part due to geographic differences as exposure to infection depends on what organisms are endemic to a region.[22] While European trials show culture-negative rates of 7% to 12% of endocarditis cases,[11,23] developing countries reveal much higher rates with Latin American cases near 20%, and case series in South Africa and Algeria reporting rates as high as 55% to 56%.[15,12,24] Zoonotic organisms, in particular *C burnetii* and *Bartonella* species, are common in these studies and cause 50% of culture-negative endocarditis.[10]

Coxiella burnetii causes Q fever, which commonly presents as self-limited flu-like illnesses in epidemic settings but can also result in pneumonia, hepatitis, and endocarditis if the infection becomes chronic.[25] Cultures are ineffective, and serology remains the standard for diagnosis. Seroconversion occurs between 1 and 2 weeks, with 90% seropositive by the third week. Levels of immunoglobulin G antibodies 1:800 or greater are consistent with chronic infection. *Coxiella* endocarditis is more common in southern Europe and Northern Africa, with rates as high as 30% in Southern France.[10]

To date, 7 *Bartonella* species have been reported to cause endocarditis, but *Bartonella quintana* followed by *Bartonella henselae* accounts for the vast majority of cases. *B quintana*, the cause of trench fever, has a reservoir in humans and body lice. *B henselae,* the agent of cat scratch disease, relies on cats and cat fleas as a reservoir.[26,27] Cultures are rarely successful, so the diagnosis is typically made with positive *Bartonella* serologies, which cannot distinguish between the specific species due to significant cross-reactivity at the species level.

Diagnosis of Culture-Negative Endocarditis

During the initial evaluation for suspected culture-negative infective endocarditis, the clinician must establish whether the patient had any antibiotic treatment prior to blood cultures that could explain the lack of culture growth. In these cases, identifying the causative organism can be difficult. Multiplex bacterial PCRs such as Septifast (Roche Diagnostics, Mannheim, Germany) may provide an alternate mode of detection, though their sensitivity is significantly greater using valvular tissue than blood.[28,29]

If cultures remain negative, further workup should search for noninfective causes, with antinuclear antibody (ANA) and rheumatoid factor (RF) antibodies, but should also include serologies for the common bacterial causes, specifically *C burnetii* and *Bartonella* species (*B quintana* and *B henselae*). In a large study of culture-negative endocarditis, these serologies provided the highest diagnostic yield, classifying nearly 75% of those with a cause identified.[10] If serologies are nondiagnostic, specific PCRs can provide additional detection. While PCR does not improve detection of *Coxiella* over serology, Fournier and colleagues recommend individual PCRs for *Bartonella* species and *T whipplei*, as well as broad-range fungal PCRs, as these were able to identify an additional 13% of cases. Rare causes of endocarditis include the intracellular organisms *Legionella* and *Mycoplasma pneumoniae*, for which serologies can be undertaken, though the yield becomes

Table 3. Treatment Regimens for Culture-Negative Endocarditis.

Regimen		Recommended Dosage	Treatment Course
Culture-negative native valve endocarditis			
A	Ampicillin–sulbactam	12 g/d div q6 hours	4-6 weeks
	Gentamicin sulfate	3 mg/kg/d div q8 hours	4-6 weeks
B[a]	Vancomycin	30 mg/kg/d div q12 hours	4-6 weeks
	Gentamicin sulfate	3 mg/kg/d div q8 hours	4-6 weeks
	Ciprofloxicin	1000 mg/d div q12 hours	4-6 weeks
Culture-negative, suspected *Bartonella*			
	Ceftriaxone	2 g/d q24 hours	6 weeks
	Gentamicin sulfate	3 mg/kg/d div q8 hours	2 weeks
	Doxycycline	200 mg/d div q12 hours	6 weeks
Documented *Bartonella* positive			
	Doxycycline	200 mg/d div q12 hours	6 weeks
	Gentamicin sulfate	3 mg/kg/d div q8 hours	2 weeks

Abbrevitions: q12 hours, every 12 hours; q8 hours, every 8 hours.
[a] When allergic to penicillin.
[b] Adapted from Baddour et al.[30]

vanishingly small, and valvular biopsy should be considered. Valvular biopsy with histology, PCRs for bacteria and fungi, and autoimmunohistochemistry provide further diagnostic power, though still are not fully sensitive.[10,28]

Treatment in Culture-Negative Endocarditis

The dilemma posed by such cases for the physician is how to treat the patient without the guidance of an identified causative organism. Infectious Diseases Society of American (IDSA) guidelines for antibiotic treatment of infective culture-negative endocarditis recommend differentiating between patients with antibiotic use prior to blood culture collection versus those without antibiotic exposure. (Table 3) For patients with prior antibiotics, *S aureus*, *S viridans*, enterococci, and to a lesser extent HACEK organisms will continue to be the most likely culprits although gentamicin can be added to ampicillin–sulbactam for better gram-negative coverage, particularly in cases with more subacute symptoms. True culture-negative native valve endocarditis requires treatment for zoonotic and fastidious bacteria, which should include an aminoglycoside in addition to broad-spectrum gram-positive and gram-negative antibiotics. Recommended regimens (see Table 3) include (1) ampicillin–sulbactam and gentamicin or (2) vancomycin, gentamicin, and ciprofloxacin for patients unable to tolerate penicillins.[30]

Case Diagnostic Results

In our patient, the suspicion remained high for an infective culture-negative endocarditis. Despite attempts at obtaining a detailed travel and exposure history from the family to gain any potential clues to etiology, a clear infective cause remained elusive. Rheumatologic studies included negative antinuclear antibody and rheumatoid factor. Given the prevalence of *C burnetti* and *Bartonella* species in culture-negative cases, these serologies were also sent. Fifteen days after hospital admission and 8 days after being drawn and sent, *Bartonella* serologies returned at greater than 1:1024.

Bartonella Endocarditis

Discussant: Arielle Davis

Bartonella, an intracellular fastidious, gram-negative bacilli, was first documented as a cause of endocarditis[31,32] in 1993 and since then has been increasingly recognized as an important etiology of infective culture-negative endocarditis. As demonstrated by our patient, *Bartonella* endocarditis typically affects middle-aged men. In the largest series of 101 patients with *Bartonella* endocarditis, the mean age (standard deviation) was 50 years (15), and 85% were men.[33] Risk factors for *B quintana* include alcoholism, homelessness, and contact with body lice, while those for *B henselae* include contact with cats, cat fleas, and prior valvular heart disease.[26,34] Our patient did not have any of these identified risk factors, including no family cats.

Patients classically present with subacute, indolent, and nonspecific symptoms. Fever is present in 83%. Vegetations due to *Bartonella* are visible on echocardiogram in more than 90% of cases and have a predilection for the aortic valve.[33] Systemic embolization, including the brain, occurs in around 40% of patients.[33] Infectious intracranial aneurysms, as discovered in our patient, are seen in only 2% to 4% of endocarditis cases[3,35,36] and are particularly rare with *Bartonella* endocarditis, with only 3 previously reported cases.[34,37,38]

The widely used Duke criteria for the diagnosis of infective endocarditis (Table 1) are biased toward capturing culture-positive cases, as positive blood cultures are a major diagnostic criteria. The challenge with *Bartonella* endocarditis is that as a fastidious and slow growing organism, it is successfully cultured in only 25% to29% of cases.[26,34] *Bartonella* species often require prolonged incubation from 21 to 45 days, so holding cultures for a week or 2, as is the practice in many laboratories, may be inadequate.[39,40] Cultures performed on valve biopsy tissue offer somewhat better odds of identifying an organism but are still relatively disappointing with *Bartonella* discovered in only around 40%.[34]

Because cultures are so rarely positive, clinicians are forced to rely on alterative diagnostic measures. The most widely used methods for detecting *Bartonella* species are serologic with both indirect immunofluorescence assay and enzyme-linked immunosorbent assay. Indirect immunofluorescence titers of 1:800 or greater for immunoglobulin G antibodies to *Bartonella* species have a positive predictive value of 95% for detection of *Bartonella* species among patients with endocarditis caused by this organism.[41] Serologies are limited by known cross-reactions with Chlamydia and less commonly with *C burnetti*, although techniques such as serum adsorption or Western blotting can determine the definitive

pathogen and in the case of *C burnetti*, the degree of titer elevation can further indicate the true diagnosis.[42,43]

Molecular techniques also have value in detection of *Bartonella* species. The PCR testing, which involves broad-range amplification of 16S ribosomal RNA, can identify causative organisms of endocarditis. The PCR amplification has been trialed with serum samples to detect *Bartonella* endocarditis, but detection in the blood is hampered by low sensitivity and technical challenges.[44] More frequently utilized and better validated is PCR from cardiac valve biopsy specimens. In one series, *Bartonella* species were identified in 44 of the 45 valve samples, despite more than 60% of these cases receiving antibiotics prior to surgical resection.[34]

The optimal treatment regimen for *Bartonella* endocarditis remains unknown, as the literature is limited only to case reports and case series. These observational studies suggest that a regimen including at least 2 weeks of an aminoglycoside, such as gentamicin, have a higher recovery rate, better prognosis, and a decreased risk of relapse compared to those with other regimens.[33] Aminoglycosides likely offer this advantage because they are bactericidal, an essential element in any endocarditis regimen. In addition to 2 weeks of aminoglycoside therapy, the other antibiotics recommended for treatment of *Bartonella* endocarditis are 6 weeks of ceftriaxone in suspected cases, as it offers the advantage of covering numerous other causes including *Streptococcus* and *Staphylococcus* species and potentially adding doxycycline (Table 3). In cases of documented *Bartonella* endocarditis, IDSA guidelines recommend 6 weeks of doxycycline plus 2 weeks of gentamicin.[30]

Case Follow-Up

When *Bartonella* serologies returned, doxycycline was added to gentamicin, and the broad-spectrum antibiotics were discontinued. He completed 2 weeks of gentamicin, and a full 6-week course of doxycycline. Subsequent CTAs revealed a stable aneurysm in the right distal PCA. At the completion of antibiotic therapy for presumed *Bartonella* endocarditis, the aneurysm was still visualized on postcontrast images but had decreased in size. The decision was made to monitor its size over time, as suggested by expert opinion on the basis of small series of patients. [45-47]

His clinical course was complicated by phenytoin-induced leucopenia, bilateral deep venous thromboses despite prophylactic heparin, and later heparin-induced thrombocytopenia. He was cautiously anticoagulated, initially with heparin and ultimately warfarin without bleeding complications.

Six months after admission, he was awake, intermittently following simple verbal commands and not vocalizing. He was breathing spontaneously, protecting his airway, and relied on a gastrostomy tube for nutrition. He had limited spontaneous movements of his limbs and had developed increased tone and contractures despite continued low intensity physical therapy and was fully dependent on around the clock nursing care.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Keywords

mycotic aneurysm, infectious aneurysm, infective aneurysm, culture-negative endocarditis, infective endocarditis, and *Bartonella* endocarditis

References

1. Pruitt AA, Rubin RH, Karchmer AW, Duncan GW. Neurologic complications of bacterial endocarditis. *Medicine*. 1978;57(4):329-343.
2. Frazee JG, Cahan LD, Winter J. Bacterial intracranial aneurysms. *J Neurosurg*. 1980;53(5):633-641.
3. Salgado AV, Furlan AJ, Keys TF, Nichols TR, Beck GJ. Neurologic complications of endocarditis: a 12-year experience. *Neurology*. 1989;39(2 Pt 1):173-178.
4. Bohmfalk GL, Story JL, Wissinger JP, Brown WE Jr. Bacterial intracranial aneurysm. *J Neurosurg*. 1978;48(3):369-382.
5. Venkatesh SK, Phadke RV, Kalode RR, Kumar S, Jain VK. Intracranial infective aneurysms presenting with haemorrhage: an analysis of angiographic findings, management and outcome. *Clin Radiol*. 2000;55(12):946-953.
6. Peters PJ, Harrison T, Lennox JL. A dangerous dilemma: management of infectious intracranial aneurysms complicating endocarditis. *Lancet Infect Dis*. 2006;6(11):742-748.
7. Salgado AV, Furlan AJ, Keys TF. Mycotic aneurysm, subarachnoid hemorrhage, and indications for cerebral angiography in infective endocarditis. *Stroke*. 1987;18(6):1057-1060.
8. Kojima Y, Saito A, Kim I. The role of serial angiography in the management of bacterial and fungal intracranial aneurysms–report of two cases and review of the literature. *Neurol Med Chir*. 1989;29(3):202-216.
9. Benito N, Miro JM, de Lazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. *Annal Intern Med*. 2009;150(9):586-594.
10. Fournier PE, Thuny F, Richet H, et al. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. *Clin Infect Dis*. 2010;51(2):131-140.
11. Hoen B, Selton-Suty C, Lacassin F, et al. Infective endocarditis in patients with negative blood cultures: analysis of 88 cases from a one-year nationwide survey in France. *Clin Infect Dis* 1995;20(3):501-506.
12. Benslimani A, Fenollar F, Lepidi H, Raoult D. Bacterial zoonoses and infective endocarditis, Algeria. *Emerg Infect Dis*. 2005;11(2):216-224.
13. Houpikian P, Raoult D. Blood culture-negative endocarditis in a reference center: etiologic diagnosis of 348 cases. *Medicine*. 2005;84(3):162-173.

14. Lamas CC, Eykyn SJ. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years. *Heart*. 2003;89(3):258-262.
15. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Inter Med*. 2009;169(5):463-473.
16. Que YA, Moreillon P. Infective endocarditis. *Nat Rev Cardiol*. 2011;8(6):322-336.
17. Slipczuk L, Codolosa JN, Davila CD, et al. Infective endocarditis epidemiology over five decades: a systematic review. *PloS one*. 2013;8(12): e82665.
18. Li J, Sexton D, Mick N, et al. Proposed Modifications to the Duke Criteria for the Diagnosis of Infective Endocarditis. *Clinical Infectious Diseases*. 2000;30:633-638.
19. Lepidi H, Durack DT, Raoult D. Diagnostic methods current best practices and guidelines for histologic evaluation in infective endocarditis. *Infect Dis Clin North Am*. 2002; 16(2):339-361, ix.
20. Pierrotti LC, Baddour LM. Fungal endocarditis, 1995-2000. *Chest*. 2002;122(1):302-310.
21. Tacke D, Koehler P, Cornely OA. Fungal endocarditis. *Curr Opin Infect Dis*. 2013;26(6):501-507.
22. Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. *Clin Microbiol Rev*. 2001;14(1):177-207.
23. Werner M, Andersson R, Olaison L, Hogevik H. A clinical study of culture-negative endocarditis. *Medicine*. 2003;82(4):263-273.
24. Koegelenberg CF, Doubell AF, Orth H, Reuter H. Infective endocarditis in the Western Cape Province of South Africa: a three-year prospective study. *QJM*. 2003;96(3):217-225.
25. Raoult D, Marrie T. Q fever. *Clin Infect Dis*. 1995;20(3): 489-495; quiz 496.
26. Raoult D, Fournier PE, Drancourt M, et al. Diagnosis of 22 new cases of Bartonella endocarditis. *Ann Intern Med*. 1996;125(8): 646-652.
27. Raoult D, Roblot F, Rolain JM, et al. First isolation of Bartonella alsatica from a valve of a patient with endocarditis. *J Clin Microbiol*. 2006;44(1):278-279.
28. Breitkopf C, Hammel D, Scheld HH, Peters G, Becker K. Impact of a molecular approach to improve the microbiological diagnosis of infective heart valve endocarditis. *Circulation*. 2005; 111(11):1415-1421.
29. Casalta JP, Gouriet F, Roux V, Thuny F, Habib G, Raoult D. Evaluation of the LightCycler SeptiFast test in the rapid etiologic diagnostic of infectious endocarditis. *Eur J Clin Microbiol Infect Dis*. 2009;28(6):569-573.
30. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111(23): e394-434.
31. Spach DH, Callis KP, Paauw DS, et al. Endocarditis caused by Rochalimaea quintana in a patient infected with human immunodeficiency virus. *J Clin Microbiol*. 1993;31(3):692-694.
32. Daly JS, Worthington MG, Brenner DJ, et al. Rochalimaea elizabethae sp. nov. isolated from a patient with endocarditis. *J Clin Microbiol*. 1993;31(4):872-881.
33. Raoult D, Fournier PE, Vandenesch F, et al. Outcome and treatment of Bartonella endocarditis. *Arch Intern Med*. 2003;163(2): 226-230.
34. Fournier PE, Lelievre H, Eykyn SJ, et al. Epidemiologic and clinical characteristics of Bartonella quintana and Bartonella henselae endocarditis: a study of 48 patients. *Medicine*. 2001; 80(4):245-251.
35. Frazee JG, Cahan LD, Winter J. Bacterial intracranial aneurysms. *J Neurosurg*. 1980;53(5):633-641.
36. Pruitt AA, Rubin RH, Karchmer AW, Duncan GW. Neurologic complications of bacterial endocarditis. *Medicine (Baltimore)*. 1978;57(4):329-343.
37. de La Blanchardiere A, Fournier PE, Haustraete E, du Cheyron D, Lepage O, Verdon R. Infective endocarditis due to Bartonella henselae following a rupture of a cerebral aneurysm. *Med Mal Infect*. 2009;39(6):394-396.
38. Martin L, Vidal L, Campins A, et al. Bartonella as a cause of blood culture-negative endocarditis. Description of five cases. *Rev Esp Cardiol*. 2009;62(6):694-697.
39. Koehler JE, Quinn FD, Berger TG, LeBoit PE, Tappero JW. Isolation of Rochalimaea species from cutaneous and osseous lesions of bacillary angiomatosis. *New Engl J Med*. 1992; 327(23):1625-1631.
40. Maurin M, Raoult D. Bartonella (Rochalimaea) quintana infections. *Clin Microbiol Rev*. 1996;9(3):273-292.
41. Fournier PE, Mainardi JL, Raoult D. Value of microimmunofluorescence for diagnosis and follow-up of Bartonella endocarditis. *Clin Diagn Laboratory Immunol*. 2002;9(4):795-801.
42. La Scola B, Raoult D. Serological cross-reactions between Bartonella quintana, Bartonella henselae, and Coxiella burnetii. *J Clin Microbiol*. 1996;34(9):2270-2274.
43. Maurin M, Eb F, Etienne J, Raoult D. Serological cross-reactions between Bartonella and Chlamydia species: implications for diagnosis. *J Clin Microbiol*. 1997;35(9):2283-2287.
44. Zeaiter Z, Fournier PE, Greub G, Raoult D. Diagnosis of Bartonella endocarditis by a real-time nested PCR assay using serum. *J Clin Microbiol*. 2003;41(3):919-925.
45. Kundra SN. Management of intracranial infectious aneurysms: a series of 16 cases. *Neurosurgery*. 2003;53(1):245-246; author reply 246.
46. Chun JY, Smith W, Halbach VV, Higashida RT, Wilson CB, Lawton MT. Current multimodality management of infectious intracranial aneurysms. *Neurosurgery*. 2001;48(6):1203-1213; discussion 1213-1204.
47. Corr P, Wright M, Handler LC. Endocarditis-related cerebral aneurysms: radiologic changes with treatment. *AJNR*. 1995; 16(4):745-748.